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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/728,051
Filing Date: December 04, 2003
Appellant(s): CAPLAN, MICHAEL J.

Katherine Nicole Clouse
For Appellants

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 1, 2010 appealing from the Office action mailed January 26, 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner has no comment on the Appellant's statement of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 34-45 are on appeal, which can be found in amendment filed October 16, 2008 and claims appendix of the Brief.

(4) Status of Amendments After Final

The examiner has no comment on the Appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the Appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the Appellant's brief.

(8) Evidence Relied Upon

WO 99/38978	August 1999
5,888,799	3-1999
WO 9214487	9-1992
6,270,723	10-1998
3,097,141	7-1963

Fenton et al, J National Cancer Institute 87(24): 1853-1861, December 1995

Vrtala et al, Int Arch Allergy Immunol 107: 290-294, 1995

Leclerc et al, J Immunology 144(8): 3174-3182, 1990

Komanapalli et al, Appl Microbil Biotechnol 49: 766-769, 1998

Ingram et al, J Bacteriology 144(2): 481-488, Nov 1980

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

1. Claims 34-43 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (of record, issued March 30, 1999; PTO 892), US Pat No. 3,097,141 (of record, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892).

The WO 99/38978 publication teaches production of recombinant modified allergen such as modified peanut allergen Ara h1 (Table 4), modified peanut allergen Ara h2 (Table 2) and modified peanut allergen (Table 6), see reference page 10, lines 10-16, Table 4-6, in particular. The recombinant modified allergen is expressed in host cell such as bacteria *E coli* strain BL21 (DE3), see page 10, line 13, page 16, line 29, in particular. The WO 99/38978 publication teaches a pharmaceutical composition comprising *E coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2 and Ara h3 where the center of one or more amino acid present in IgE binding sites of Ara h1, Ara h2 and Ara h3 have been substituted with neutral or hydrophilic amino acid or lacks a portion of the wild-type peanut allergen such that the modified peanut allergens have reduced binding to IgE as compared to the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, claims 1-7 of the WO 99/38978 publication, in particular). The reference wild-type Ara h3 allergen of SEQ ID NO: 6 is encoded by the reference nucleotide sequence of SEQ ID NO: 5, which is identical to the claimed SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular). The reference IgE binding sites of Ara h1, Ara h2 and Ara h3 are shown in Table 4 at page 23, Table 5 at page 24 and Table 6 at page 24, respectively. The reference wild-type Ara h1 of SEQ ID NO: 2 is encoded by the reference SEQ ID NO: 1. The reference wild-type Ara h2 of SEQ ID NO: 4 is encoded by the reference SEQ ID NO: 3. The reference further teaches a method of making modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the modified peanut allergen or portion thereof has at least one amino acid that has been deleted or substituted within the IgE binding sites such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, claims 29-in particular). The reference modified peanut allergen is deemed to be encapsulated inside the dead *E coli* because the recombinant modified protein is expressed as inclusion bodies which located in the cytoplasm since it must be solubilized with urea (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular). The reference's modified peanut allergens Ara h1, Ara h2 and Ara h3 are identical to the ones incorporated by reference to 09/141,220. The WO 99/38978 publication teaches the

modified peanut allergen is safe and efficacious for treating peanut allergy (see page 2, lines 21, claim 36 of the publication, in particular). The advantage of having IgE binding sites converted to non-IgE binding sites by masking the site or by single amino acid substitution within the center of IgE binding would be useful for immunotherapy (see abstract, page 10, in particular).

The claimed invention differs from the teachings of the reference only in that the pharmaceutical composition wherein the *E coli* is dead instead of live *E coli* expressing modified peanut allergen and the *E coli* was killed by heat.

Fenton et al teach a pharmaceutical composition comprising dead *Escherichia coli* that have been engineered to express recombinant modified ras protein bearing a Gln to Leu mutation at residue 61 and a pharmaceutical carrier such as Hanks Balance Salt solution or HBSS (see page 1855, col. 1, Immunization with heat-killed bacteria, in particular). The reference *E coli* were heat-killed by incubation at 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). The reference recombinant Ras protein obviously located in side the *E coli* such as inclusion bodies located within the cytoplasm given the purification of Ras protein must be disrupted with sonification (see page 1854, col. 2, Purification of Ras proteins, in particular). Fenton et al further teach antigen presenting cell such as macrophage can phagocytose genetically engineered *E coli* and present the recombinant modified protein derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen specific immunity by modulating immune response to Th1 as measured by cytokines IL-2, IFNγ secreted and granuloma formation at the vaccine site (see page 1857, col. 2, full paragraph, page 1860, col. 2, second full paragraph, in particular).

Vrtala et al teach the use of recombinant non-pathogenic *Salmonella* genetically engineered to express modified birch pollen allergen Bet vI localized to the cytoplasm of *Salmonella* and mice fed with Salmonella expressing modified Bet vI can develop a Bet vI allergen specific Th1 immune response (see page 293, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen without having the need for extensive protein purification (see page 293, col. 2, in particular). However, there are a number of technical and ethical problems before such *live* allergy vaccines could be used for therapy of type I allergy in patients (see page 293, col. 2, in particular).

The '799 patent teaches the use of *E coli* as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in

particular). The reference *E coli* can be viable or non-viable upon the death of the micro, the antigen will be made available by the carrier and releases cytoplasmic and/or periplasmic antigens/ allergens (see col. 9, lines 3-40, in particular). The '799 patent teaches the antigen or allergen of interest in the *E coli* can be engineered to transport across the *E coli* cytoplasmic membrane end ended up in the periplasmic space (see col. 14, line 29-31, in particular). The bacterial cell is formulated for administered orally in enteric-coated capsules (see col. 13, line 4-6, in particular).

The '141 patent teaches a method of modifying anaphylactogens to reduce toxicity and to prevent hypersensitivity while retaining antigenicity of *E coli* by heating *E coli* from about 50 to 100 °C to kill the bacteria (see col. 1, lines 8-65, col. 2, line 1-10, in particular). The '141 patent further teaches *E coli* can be killed by chemical treatment such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide H_2O_2 (see col. 1, line 58, in particular).

Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant *E coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen in the periplasm instead of cytoplasm and a pharmaceutical acceptable carrier such as PBS (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Leclerc et al teach good antibody responses were development after injection of heat-killed bacteria by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the *E coli* that is expressed the modified peanut allergen Ara h1, Ara h2 and Ara h3 with reduced ability to bind to or cross-link IgE of the WO 99/38978 publication as an allergen carrier for induction of tolerance as taught by the '799 patent by killing the *E coli* bacteria by heating from about 50 to 100°C as taught by Fenton or the '141 patent or Leclerc et al or killing the bacteria by oxidizing agent such as Hydrogen peroxide as taught by the '141 patent to avoid any ethical issues when administering live bacteria and without the need for extensive protein purification using such bacteria for treating allergy as taught by Vrtala et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to modify peanut allergen because peanut is highly anaphylactic and the advantage of having IgE binding sites converted to non-IgE binding sites by *masking* the IgE site or by single amino acid substitution within the center of IgE binding site of the peanut protein

such as Ara hl, Ara h2 and Ara h3 would be useful for immunotherapy as taught by the WO 99/38978 publication (see abstract, page 10, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use heat killed bacteria *E coli* expressing modified food allergen because Vrtala et al teach killing the microorganism that expressed modified allergen can avoid the ethical problems associated with using *live* microorganism for allergy vaccines or therapy of type I allergy in patients (see page 293, col. 2, in particular). Vrtala et al teach the advantage of using bacteria transformed with any cDNA coding for the respective allergen is not having the need for extensive protein purification (see page 293, col. 2, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use killed *E coli* bacteria as vaccine carrier because Fenton et al teach heat-killed recombinant *E coli* is useful as a vaccine since antigen presenting cell such as macrophage can phagocytose the bacteria *E coli* and present the peptides derived from bacterially synthesized products in association with MHC class I molecule to elicit antigen/allergen specific immunity, and to modulate immune response to Thl as measured by cytokines IL-2, IFN_7 secreted (see page 1857, col. 2, full paragraph, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use heat-killed *E coli* bacteria because Leclerc et al teach good antibody responses were development after injection of heat-killed *E coli* bacteria expressing the antigen of interest by the s.c. or i.v. route (see page 3177, col. 1, Figure 3, Table II, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to use bacteria *E coli* as a vaccine carrier because the '799 patent teaches microorganism such as *E coli* can be use as an antigen or allergen carrier for treating allergy by induction of tolerance (see entire document, col. 9, lines 59 bridging col. 10, lines 6, in particular).

One having ordinary skill in the art at the time the invention was made would have been motivated with the expectation of success to kill bacteria with heat because the ' 141 patent teaches heat killing *E coli* can reduce toxicity and preventing hypersensitivity while retaining antigenicity of E *coli* (see col. 1, lines 8-65, col. 2, lines 1-10, in particular). From the combined

teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since recombinant production of modified peanut allergen in *E coli* is known at the time of the invention and combining the prior art elements of using dead *E coli* (killed by heat or chemical) expressing modified allergen in periplasm (encapsulated) or cytoplasm as a carrier for induction of tolerance is desirable and have been predictable at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention. Obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007).* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

2. Claims 44-45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/38978 publication (of record, Aug 1999, PTO 1449) in view of Fenton et al (of record, J National Cancer Institute 87(24): 1853-1861, December 1995; PTO 892), Vrtala et al (of record, Int Arch Allergy Immunol 107: 290-294, 1995; PTO 1449), US Pat No 5,888,799 (of record, issued March 30, 1999; PTO 892), US Pat No. 3,0997, 141 (of record, issued July 9, 1963; PTO 892) and Leclerc et al (of record, J Immunology 144(8): 3174-3182, 1990; PTO 892) as applied to claims 34-43 mentioned above and further in view of WO 92/14487 (of record, published September 1992; PTO 892) and US Pat No 6,270,723 (of record, filed Oct 2, 1998; PTO 892), Komanapalli et al (of record, Appl Microbil Biotechnol 49: 766-769, 1998; PTO 892) and/or Ingram et al (of record, J Bacteriology 144(2): 481-488, Nov 1980; PTO 892).

The combined teachings of the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and Leclerc et al have been discussed supra.

The claimed invention in claim 44 differs from the combined teachings of the references only in that the composition wherein the *E coli* were killed by chemical treatment instead of heat.

The claimed invention in claim 45 differs from the combined teachings of the references only in that the composition wherein the *E coli* was killed using a chemical selected from the group consisting of bleach, ozone, and alcohols instead of heat.

The WO 92/14487 publication teaches a method of safely killing *E coli* bacteria expressing various colonization factor antigens by chemical treatment such as mild or diluted formalin-treated *E coli* for use as a whole cell vaccine (see page7-8, page 19, line 26, in particular). The WO 92/14487 publication teaches the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria and at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as greater stability of the antigen against degradation in the intestinal milieu (see page 8, lines 7-9, in particular).

The '723 patent teaches various methods of killing *bacteria* by chemical treatment such as alcohol (see col. 1, line 21, in particular), bleach (see col. 10, line 39-40, in particular) or pressure sterilization (ozone) to inactivate bacteria such as *E coli* for pharmaceutical composition (see col. 11, lines 42-67, col. 15, line 8, in particular). The '723 patent teaches these methods can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular).

Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* while oxygen gas has no effect (see page 767, col. 2, results, Fig. 1, in particular). Ozone induced lipid oxidation in *E coli* and leakage of cytoplasmic contents (see abstract, see Figs 5 & 6, in particular).

Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). Ingram et al teach increasing concentrations of alcohol such as ethanol and hexanol progressively inhibits the growth of *E coli* and hexanol was a much more potent inhibitor of growth than was ethanol (see page 482, col. 2, in particular). Ingram et al teach ethanol prevented the assembly of cross-linked peptidoglycan while hexanol did not inhibit such cross-linking, see page 485, col. 2, in particular.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to kill any recombinant modified peanut allergen producing *E. coli* for a pharmaceutical composition given the highly anaphylactic nature of the peanut allergen as taught by the WO 99/38978 publication where the killing of bacteria by means chemical treatment such as mild or diluted formalin-treatment as taught by the WO 92/14487 publication or diluted alcohol or diluted bleach as taught by the '723 patent or alcohol as taught by Ingram or by ozone as taught by Komanapalli et al to preserve the immunogenic property of inactivated bacteria as taught by the WO 92/14487 publication.

One having ordinary skill in the art would have been motivated to do this because the advantage of formalin-killed bacteria is that it would safely kill the *E coli* bacteria while at the same time preserving the antigenic properties of the antigen expressed in *E coli* as well as maintaining greater stability of the antigen against degradation in the intestinal milieu as taught by the WO 92/14487 publication (see page 8, lines 7-9, in particular). One having ordinary skill in the art would have been motivated to do this because the '723 patent teaches chemical treatment such as iodine, bleach, ozone, or alcohol can improve the safety of vaccine or any product used by patient (see col. 8, lines 26-67, col. 9, lines 1-15, in particular). One having ordinary skill in the art would have been motivated to do this because Ingram et al teach alcohols and other amphipathic molecules have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). One having ordinary skill in the art would have been motivated to do this because Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* (see page 767, col. 2, results, Fig.

1, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

(10) Response to Argument

At page 10 of the Brief, Appellant states that the Examiner does not appear to have considered Appellant's argument in the Response to Office Actions that were filed on November 1, 2006, July 30, 2007 and October 16, 2008.

Inspection of the record indicates the following: First of all, there were no amendments or arguments filed dated November 1, 2006 and July 30, 2007 as asserted. Secondly, there was an RCE filed on November 3, 2006. The arguments submitted with said RCE were fully considered and responded in Office Action mailed January 31, 2007, see pages 22-24 and pages 28-29. Finally, with respect to arguments filed October 16, 2008, Appellant's arguments were fully considered and responded in Final Office Action mailed January 26, 2009, see pages 7-15. While the format of the response may not have been addressed to Appellant's liking (pages 11-12 of the Brief), nevertheless, the arguments have been considered, see pages 7-15 of Final Office Action mailed January 26, 2009 and explained further below.

With respect to the argument that the protein expressed in *E coli* is a different protein and not a modified peanut allergen as recited in present claims (First paragraph at page 5 of the response filed October 16, 2008), while the WO 99/38978 exemplified making of peanut Ara 2 protein in *E coli* strain BL21 (DE3), the WO 99/38978 publication also teaches recombinantly modified peanut expressed in bacteria *E coli* (see claims 14 and 27 of WO 9938978, page 4, lines 10-17, in particular).

With respect to the argument that the WO/38978 publication does not teach modified peanut allergen "encapsulated inside" dead *E coli* (Second paragraph of response filed October 16, 2008; second paragraph at page 15 of the Brief), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. The WO/38978 publication teaches modified peanut allergen having reduced IgE binding and is expressed in recombinant host such as *E coli* bacteria strain BL21 (DE3) (see entire document, claims 14 and 27, pages 16, lines 29, in particular). While the publication does not explicitly state that the modified allergen is encapsulated inside the cell, that the purified protein must be lysed in denaturing binding buffer would suggest to one of ordinary skill in the art at the time the invention was made that the protein is encapsulated inside (not secreted, but expressed as inclusion bodies), see page 16, line 31-32 of WO 99/38978, in particular. In fact, the instant specification uses the same *E coli* strain BL21 (DE3) to express the peanut allergen (see page 37, lines 21-28, in particular). If Appellant's modified peanut allergen is encapsulated inside the bacteria, so does the teachings of the reference.

While the WO 99/38978 does not teach dead *E coli* as a pharmaceutical composition, Fenton et al teach heat-killed bacteria *E coli* expressing protein of interest by raising the temperature to 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular). Similarly, the '799 patent also teaches non-viable *E coli* expressing allergen as a carrier for treating allergy (see col. 9, lines 59 bridging col. 10, lines 6, col. 9, lines 3-40, in particular). Likewise, the '141 patent teaches dead *E coli* expressing modified anaphylactogens (allergen) to prevent hypersensitivity by heating the *E coli* from about 50 to 100 °C (see col. 1, lines 8-65, col. 2, lines 1-10, in particular) or by rendering the *E coli* dead by chemicals such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide (see col. 1, lines 58, in particular). Likewise, Leclerc et al teach pharmaceutical composition comprising

dead *E coli* expressing antigen of interest such as hepatitis B virus antigen that is encapsulated inside the periplasm instead of the cytoplasm of *E coli* (see page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Reasons as to why one of ordinary skill in the art would have been motivated with the expectation of success to use a pharmaceutical composition comprising dead bacteria expressing modified allergens have also been provided by Vrtala et al (see reference Vrtala et al page 293, col. 2, in particular) and pages 9-10 of Office Action mailed January 26, 2009. As such, the rejection is proper.

With respect to the argument that the '978 inventor used urea in purifying a protein does not mean that the protein is encapsulated within the bacteria (First paragraph at page 5 of the response filed October 16, 2008; page 15 of the Brief), the specification does not define how the modified allergen encapsulated within the *E coli*. The broadest reasonable interpretation of such is that the claims read on modified peanut allergen being expressed in the periplasmic space or as inclusion body such that the allergen are not being secreted. While the WO 99/38978 publication does not explicitly state that the modified allergen is encapsulated inside the cell, that the purified protein must be in denaturing binding buffer would suggest to one of ordinary skill in the art at the time the invention was made that the protein is encapsulated inside (not secreted), see page 16, line 31-32 of WO 99/38978, in particular. In fact, instant specification uses the same *E coli* strain BL21 (DE3) and the same plasmid to express the peanut allergen, see page 37, lines 21-28, in particular). If Appellant's modified peanut allergen expressed in the same *E coli* strain BL21 (DE3) is encapsulated inside the bacteria, so does the teachings of the reference.

Even if the WO 99/38978 does not teach modified peanut allergen expressed within (encapsulated within) the *E coli*, Leclerc et al teach how to make recombinant protein expressed within the periplasm (not secreted) instead of cytoplasm and then render the *E coli* dead by heat as a pharmaceutical composition (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Likewise, the '799 patent teaches how to make recombinant allergen expressed within the

periplasmic space (encapsulated within) and not release to the cytoplasm (see col. 9, lines 3-40, in particular).

With respect to the argument that '978 publication teaches isolating protein from dead *E coli*, they are not preparing the dead *E coli* as a pharmaceutical composition as recited in the present claims (third paragraph at page 5 of the response filed October 16, 2008; third paragraph at page 15 of the Brief), as stated earlier, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. The '978 publication does teach bacteria such as *E coli* expressing modified peanut allergens such as Ara h1, Ara h2 and Ara h3 and the use of organism expressing modified peanut allergens as a pharmaceutical composition in addition to isolated modified peanut allergens (see pages 8-12, claims 14 and 27, in particular). While the WO99/38978 publication does not teach pharmaceutical composition comprising dead *E coli* expressing modified peanut allergens within the bacteria, the concept of using dead *E coli* as a vaccine vehicle in a pharmaceutical composition is known in the art. For example, the '141 patent teaches dead *E coli* expressing modified anaphylactogens (allergen) to prevent hypersensitivity by heating the *E coli* from about 50 to 100 °C (see col. 1, lines 8-65, col. 2, lines 1-10, in particular) or by render the *E coli* dead by chemical such as phenol (see col. 1, line 31, in particular) or oxidizing agent such as hydrogen peroxide (see col. 1, lines 58, in particular). Likewise, Leclerc et al teach the use of dead *E coli* expressing antigen of interest such as hepatitis B virus antigen that is encapsulated inside the periplasm instead of the cytoplasm of *E coli* as a pharmaceutical composition (see page 3175, paragraph bridging col. 1 and 2, abstract, in particular). Fenton et al teach heat-killed bacteria *E coli* expressing protein of interest as a pharmaceutical composition by raising the temperature to 56°C for 40 minutes (see page 1855, col. 1, second paragraph, in particular).

At page 14 of the Brief, Appellant argues that the '978 publication does not teach modified Ara h2 can be produced recombinantly and certainly does not describe what kind of cells would be used. On the contrary, the WO 99/38978 teaches modified Ara h2 can be produced recombinantly in bacteria such as *E coli* (see claims 14, 27 and 29 of WO 99/38978 publication, page10, lines 10-14, page 16, lines 28-30, in particular). Further, the method of producing any protein of interest recombinantly using bacteria such as *E coli* is known in the art at the time the invention was made. For example, Fenton et al teach how to make recombinant protein in *E coli* (see page 1854, Purification of Ras proteins, in particular). Likewise, the '799 patent teaches recombinant DNA techniques are sufficiently well known and widespread so as to be considered routine for making recombinant protein such as allergen (see col. 10, lines 32 through col. 11, lines 19, in particular).

At page 15 of the Brief, Appellant argues that the inventors are not preparing dead *E coli* so that that the dead *E coli* itself can be formulated into a pharmaceutical composition, and that the '978 publication as a whole had no appreciation that the produced protein allergens could be useful except if and until they were isolated from bacteria cells (see e.g., Examples 4 and 5), had the '978 publication teaches all the limitations, this rejection would have been rejected under 35 U.S.C 102(a) instead of under 35 U.S.C. 103 (a). While the WO 99/38978 publication does not teach the limitation dead *E coli*, Fenton et al teach the use of dead *E coli* which have been expressed protein of interest as a pharmaceutical composition (see page 1855, col. 1, second paragraph, in particular). Likewise, Leclerc et al teach a pharmaceutical composition comprising heat-killed recombinant E *coli* expressing any antigen of interest such as foreign poliovirus epitopes or hepatitis B virus antigen as a pharmaceutical composition (see entire document, page 3175, paragraph bridging col. 1 and 2, abstract, in particular). The choices of how to render the bacteria dead are taught by many of the secondary references cited. For example, Fenton et al teach the live *E coli* can be rendered dead by heat treatment such as incubation at 56 °C for 40 minutes,

see page 1855, left col., Immunization with heat-killed bacteria, in particular. Likewise, the '141 patent teaches the optimal temperature for heat killed *E coli* is from about 50 to 100 °C, preferably 56 °C (see col. 3, lines 65, col. 2, line 1-3, in particular) or by chemical such as phenol (see col. 1, line 31, in particular). Likewise, Lecberc et al teach dead recombinant *E coli* expressing a protein of interest as a pharmaceutical composition where the bacteria are rendered dead by heat dated back to 1990 (see page 3178, Table II, in particular).

At page 16 of the Brief, Appellant argues that Fenton et al as a whole relate to composition and methods that result in a mutation-specific immune response and teach away from immunization using cells comprising modified allergens (see Response submitted on July 30, 2007). Again, the Office record shows no response was submitted on July 30, 2007 in the instant application. Only a notice of Appeal and extension of time were filed. As such, no response on the part of the Examiner is required. Once again, Fenton et al is cited for the teachings of *heat-killed E coli* expressing protein of interest as a pharmaceutical composition. While Fenton et al does not teach *E coli* expressing modified peanut allergens, the WO 99/38978 publication teaches recombinant *E coli* expressing modified peanut allergens (see claims 14, 27, 29 of the WO 99/38978, page 16, line 28-30, in particular). The WO 99/38978 publication teaches "modified allergen will typically be made using recombinant technique", see page 10, lines 10-14, in particular.

At last paragraph page 16 of the Brief, Appellant argues that Fenton teaches away from immunization using cells comprising modified allergens, one ordinary skill in the art one of ordinary skill in the art looking at Fenton would certainly conclude that immunizing an individual with a modified allergen would not result in protective immunity against multiple variants of that allergen *(e.g.,* wild type allergen, other modified allergens), it is noted that the claims are drawn to pharmaceutical composition;

the rejected claims are NOT drawn to a *method of immunizing* an individual against wild type allergen and/or other modified allergen variants as argued.

At first paragraph page 17 of the Brief, Appellant states that "Vrtala *as a whole* relate to compositions comprising *live Salmonella,* not *dead E. coli* (see Response submitted on February 29, 2008). As discussed in the Response submitted on July 30, 2007 (and subsequently ignored by the Examiner)", this allegation is unfounded as the Office record shows no response were ever submitted on July 30, 2007 in instant case. Contrary to Appellant's assertion that response submitted on February 29, 2008 was ignored, the arguments have been fully considered as indicated at page 6, second paragraph through 15, particularly page 15 for secondary references, see Final Rejection dated January 26, 2009. Again, while Vrtala does not teach dead *E coli*, the combined teachings of the WO 99/38978 publication Fenton et al, Vrtala et al, the '799 patent, the '141 patent and/or Leclerc et al as a whole would have produced the claimed pharmaceutical comprising dead *E coli* comprising any modified peanut allergen Ara h1, Ara h2 or Ara h3 encapsulated within the dead *E coli* and a pharmaceutical acceptable carrier.

The motivation as to why one of ordinary skill in the art would want to use dead bacteria expressing any allergen of interest is because of the ethical problems associated with using live microorganism as allergy vaccine is provided by Vrtala et al, see p 293, right col., in particular. Another reason as to why one of ordinary skill in the art at the time the invention was made to use dead bacteria is because of convenient, it does not have the need for extensive protein purification using bacteria transformed with any cDNA encoding the modified allergen of interest as taught by Vrtala et al, see page 293, right col. in particular.

With respect to Appellant's argument that Vrtala do not even mention the possibility of using dead bacteria as vaccines, it is noted that the rejection is based on a combination of references. Fenton et

al teach the use of dead bacteria, *E coli* in particular, as vaccines, see page 1855, left col. Immunization with heat-killed bacteria, in particular. Likewise, Leclerc et al teach the use of dead bacteria such as *E coli* as vaccine, see page 3175, left col., first full paragraph, page 3178, in particular.

At second paragraph page 17 of the Brief, Appellant argues that the '799 patent as a whole teaches live bacteria, the '799 patent teaches if a live carrier microbe is used, the antigen needs to become available to the animal's immune system and this may be accomplished when the microbes dies so that the antigen or allergen molecules are released (see col. 9, lines 3-7, col. 9, lines 59 through col. 10, line 1, in particular). Even if the '799 patent does not teach dead bacteria *E coli*, Fenton et al teach dead *E coli* as a pharmaceutical composition, see page 1855, left col., Immunization with heat-killed bacteria, in particular. Likewise, Leclerc et al teach dead recombinant *E coli* as a pharmaceutical composition where the bacteria are rendered dead by heat dated back to 1990 (see page 3178, Table II, in particular).

With respect to the argument that Appellant does not see how these teachings of the '799 patent would motivate the skilled person to prepare dead *E coli* that include encapsulated allergens, the '799 patent teaches allergen can be expressed in any desired organism, see col. 11, line 5-10, col. 9, lines 59-67, in particular. The '799 patent teaches the use of *E coli* defective in transport so that the expressed protein allergens of interest that are end up in the periplasmic space (encapsulated within the bacteria), see col. 14, lines 26-31, in particular. Evidentiary reference Leclerc et al teach gram-negative bacteria are surrounded by two membranes: the outer membrane which is in direct contact with the external medium and the cytoplasmic membrane which encloses the cytoplasm. Between the two membranes there is aqueous compartment, the periplasm, which contain a number of soluble proteins and most of these protein can be released from the cell into the medium by osmotic shock, see paragraph bridging page 3174 and 3175, in particular. As such, any allergen of interest expressed in *E coli* that are defective in

transport where the allergen ended up in the perisplasm is considered encapsulated within the bacteria as taught by the '799 patent. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Claim terms are interpreted not only in light of the specification but also in light of the prior art. See In re Cortright, 49 USPQ2d 1464, 1467 (Fed. Cir. 1999). In this case, the specification does not define what is meant by "encapsulated within the bacteria". The broadest reasonable interpretation consistent what is known in the prior art is modified peanut allergen expressed in the periplasmic space or as inclusion bodies of *E coli*. In fact, instant specification uses the same *E coli* strain BL21 (DE3) to express the modified peanut allergen, see page 37, lines 21-28, in particular as that of the WO 99/38978 publication. If Appellant's modified peanut allergen is encapsulated inside the same bacteria *E coli*, so does the teachings of the reference. If the invention is that the bacteria are encapsulated within a device as disclosed at page 34 (but not claim), the '799 patent also teaches such device and known in the art (see col. 12, lines 59-66, in particular).

At page 18 of the Brief, Appellant argues that the Examiner using hindsight reconstruction when citing the '141 patent. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971). In this case, it is common knowledge within the level of one of ordinary skill in the vaccine art at the time the claimed invention was made as how to render *E coli* dead by many ways such as heat (claim 43), which is taught by the '141 patent (see col. 1, lines 64 through col. 2, lines 6, in particular) or chemical treatment such as phenol (see '141 patent, col. 1, line 31, in particular). Likewise, Fenton et al teach the live *E coli* can be rendered dead by heat treatment

such as incubation at 56 °C for 40 minutes, see page 1855, left col., Immunization with heat-killed bacteria, in particular. Again, Lecberc et al teach live recombinant *E coli* expressing a protein of interest as a pharmaceutical composition where the bacteria are rendered dead by heat-killed (see page 3178, Table II, in particular).

At the last paragraph page 18 of the Brief, Appellant submits that claims 44 and 45 are allowable over any combination of all 10 cited references. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

At page 19 of the Brief, in contrast to Appellant's assertion that the Examiner has failed to considered the claims and the cited the references as a whole, the combined teachings of the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and Leclerc et al have been discussed supra and are incorporated here by reference. The claimed invention in claim 44 differs from the combined teachings of the references only in that composition wherein the *E coli* was killed by chemical treatment instead of heat. The claimed invention in claim 45 differs from the combined teachings of the references only in that the pharmaceutical composition wherein the *E coli* was killed using a chemical treatment such as bleach, ozone or alcohols instead of heat. However, the deficiencies of such killing of *E coli* by various chemical treatments are taught by any one of the secondary references cited therein. For example, WO 92/14487 publication teaches ways to kill *E coli* by chemical treatment such as formalin for use a whole cell vaccine to preserve the structure against degradation (see pages 7-8, lines 19, line 26, and page 8, lines 7-9). The '723 patent teaches other ways to kill bacteria (inactivate bacteria) by use of alcohol (see col. 1, lines 21, in particular), bleach (see Col. 10, lines 39-40, in

particular) or ozone for pharmaceutical composition (see col. 11, lines 42-67, col. 15, lines 8, in particular). Komanapalli et al teach ozone treatment resulted in a time-dependent decrease of cell viability of *E coli* while oxygen gas has no effect (see page 767, col. 2, results, Fig. 1, in particular). Ingram et al teach various alcohols have long been used as antimicrobial agents to prevent the growth of bacteria (see page 484, col. 2, Discussion, in particular). The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

A prior art reference from a different field may serve as analogous art if it is reasonably pertinent to the problem addressed by the application, see *In re Icon Health & Fitness,* Inc. No. 06-1573 (Fed. Cir. Aug. 1, 2007). In this case, given the little guidance in the specification, the claim did not limited the degree or manner in which the *E coli* bacteria must be killed in the claimed composition, the '723 patent teaches various ways of killing bacteria *E coli* by chemical treatment such as alcohol, bleach or ozone for pharmaceutical composition, the WO92/14487 publication teaches killing of *E coli* by chemical treatment with formalin, Komanapalli et al teach killing of *E coli* by ozone and Ingram et al teach alcohol such as ethanol and hexanol have long been used as antimicrobial agent would have led one of ordinary skill in the art to combine the teachings of the '723 patent or the WO92/14487 publication or Komanapalli et al or Ingram et al with the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and Leclerc et al to arrive at the claimed limitations. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the heat-killed process of Fenton et al or Leclerc et al for any of chemical treatment as taught by the '723 patent, the WO92/14487, Komanapalli et al or Ingram et al to render the live *E coli* expressing modified peanut allergens encapsulated within the bacteria of the WO 99/38978 dead for a pharmaceutical composition as

taught by the WO 99/38978 publication, Fenton et al, Vrtala et al, the '799 patent, the '141 patent and Leclerc et al.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, combining the prior art elements according to known methods of killing *E coli* would yield predictable results of pharmaceutical composition comprising dead *E coli.*

In this case, simple substitution of heat-killed process of Fenton et al or Leclerc et al for another known chemical process of killing bacteria *E coli* such as alcohol, formalin or ozone as taught by the '723 patent or the WO92/14487 publication or Komanapalli et al or Ingram et al would obtain predictable dead *E coli* as pharmaceutical composition at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention. Obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385*

(2007). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Phuong Huynh/

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